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(54) Title: BULK PRODUCTION AND USAGE OF HYPERPOLARIZED [129]XENON

(57) Abstract

The production and usage of hyperpolarized [129]Xenon which comprises providing solid xenon with either an internal (dissolved) or external (imbedded) nuclear spin relaxant, loading and positioning the solid xenon in a low temperature refrigerator operating in the range of 5 mK to 30 mK with a surrounding magnetic field of between about 10 and 20 Tesla enabling high xenon spin polarizations between about 10 % and 50 % to be obtained in a time of about 1–3 days owing to the properties of the relaxant, separating the xenon from the relaxant or otherwise rendering the relaxant inoperable after polarizing and thereby switching off further relaxation and insuring preservation of the polarization of the xenon in solid, liquid or gaseous form for storage or external use for long times, ranging from weeks to the order of minutes, depending on the usage conditions.

BULK PRODUCTION AND USAGE OF HYPERPOLARIZED ^{129}XENON

Background and Summary

The present invention relates to the production of Xenon for use in magnetic resonance imaging, and more specifically for the bulk production and usage of hyperpolarized ^{129}Xenon.

5   Highly spin-polarized ^{129}Xenon nuclei and ^{3}Helium nuclei offer prospects of greatly improved medical magnetic resonance imaging (MRI) as more fully discussed in *"General Review Article : Physics Today, June 1995, p. 17-18"*. It is known that the MRI contrast available with hyper-polarized ^{129}Xenon is enhanced by 5 orders of magnitude compared with the contrast obtainable with ordinary

10   equilibrium polarizations at room temperature, resulting in images of the lung cavity comparable to, or better than, those seen from protons in dense tissues. Furthermore, by exchanging polarization with protons in tissue or blood, the polarization of the latter can be enhanced in some situations so as to increase greatly the sensitivity and resolution of MRI images, which could revolutionize MRI

15   imaging techniques and open up new diagnostic applications. The exploratory medical applications thus far have been made with xenon polarized by the optical pumping technique more fully described in *"Optical Pumping Method": W. Harper et al., Phys. Rev. A29, 3092 (1984)* , which can achieve suitably high polarizations, but because polarization is produced in the gaseous phase, it is costly and not very

20   suitable for the production, storage and distribution of large quantities, which are almost certainly going to be demanded.

The general nature of the polarization methods of the present invention are related to concepts which have been developed for polarized H and D nuclei in HD molecules, for the purpose of producing polarized H and polarized D for nuclear and

25   particle physics targets, and for other uses. U.S. Patent 4,642,206 teaches these polarization processes applied to HD, but the principles rather than the particular material are the basis of the present invention and these apply to xenon and to other nuclei. In these HD and in the hyper-polarized xenon materials, a necessity is to utilize very low temperatures and high magnetic fields and spin-polarize large

amounts of material in the condensed phase. The apparatus for obtaining large

polarizations in high magnetic fields is cumbersome, and the main principle is to

polarize under conditions wherein the relaxation times are reasonably short, for

example of the order of a day, and then effect a great increase in the relaxation times

5 so that the material can be considerably warmed, and with only a modest

surrounding magnetic field, still retain for long times the polarization earlier

achieved. This core concept is the "relaxation switch", manifestations of which are

described in published journal articles: *"HD Polarized Targets": A. Honig, Q. Fan,*

X. Wei, A.M. Sandorfi and C.S. Whisnant, Nuc. Instrum. and Methods A356,

10 *39(1995)* and *"HD Polarized Targets": A. Honig et al., 12th Intl Symposium on High*

Energy Spin Physics, Amsterdam, Sept 10-14, 1996. p. 365. World Scientific, 1997,

and in the 4,642,206 patent referred to above. For the HD, one form of relaxation

switch described involves introducing a concentration of H_2 and/or D_2 impurities in a

metastable state in which the molecules have rotational angular momentum (ortho-

15 H_2 and/or para-D_2). These impurities permit rapid relaxation to occur among the

host HD molecules. One then waits for conversion of these impurities to a benign,

rotationless state, thus shutting off the relaxation and allowing the polarization to

remain for long times even at ordinary liquid helium temperatures and at modest

fields less than a Tesla, in a so-called "frozen-spin" state. In this case, the "frozen-

20 spin" occurs in a state more accessible for usage (higher T, lower B) than the state in

which the polarization is originally produced (lower T, higher B). This is unlike

many other frozen-spin processes, particularly those involving electron-nuclear

dynamic polarization, which are discussed in the literature *"12th Intl. Symposium on*

High Energy Spin Physics, Amsterdam, Sept. 10-14, 1996. p. 365. World Scientific,

25 *1997",* where the usage temperature is often lower than that used in the polarization

process. This relaxation switch process is the basis of large polarized nuclear HD

targets which are now in the process of being prepared for usage in nuclear physics

laboratories and national accelerator sites, i.e., *"LEGS Project at Brookhaven*

National Laboratory, Upton, NY; GRAAL Project at Grenoble, France". The

30 polarized D in HD also has application to nuclear fusion fuels, as do polarized

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tritium nuclei and ^{3}He nuclei, for which polarization techniques have been put forward. Another relaxation switch proposed for the HD in the aforementioned 4,642,206 patent involves introduction of radicals by irradiation or other means, which catalyze the relaxation at the polarizing conditions of very low temperature

5   and high magnetic field. The relaxation switch-off is then achieved by inducing recombination by waiting or annealing at higher temperatures, or by quick conversion to a liquid phase, carried out in a time sufficiently short so that the polarization doesn't decay before refreezing is effected. Other relaxation switches conceived of for the 'hydrogens' molecules include turning off the relaxation due to

10 impurities by effecting a change of phase, such as in D_2, where the relaxation time in the liquid phase exceeds that in the solid phase near the melting region.

It is therefore an object of this invention to provide methods of polarizing solid xenon which can result in large quantities of the hyper-polarized xenon at a lower cost and in a more favorable form than that envisaged by the conventional

15 optical pumping method.

The present invention is directed towards a polarization process for producing bulk hyper-polarized solid ^{129}Xenon in a fairly short time (less than 3 days), and several relaxation switches particularly relevant to spin-polarized ^{129}Xe, allowing its use for enhanced magnetic resonance imaging (MRI) for medical and

20 biological research applications, and for other applications as well in the gaseous phase and "frozen-spin" configuration. We also describe several configurations of the apparatus for polarizing and utilizing hyper-polarized ^{129}Xenon.

Detailed Description of the Invention

25   ^{129}Xenon is a gas at room temperature. The nucleus has a spin quantum number of ½, and a moderately large nuclear magnetic moment of -0.7726 nuclear magnetons. It can be taken up into the lungs, and absorbed into blood or tissue. It has been recognized that it has potential to be imaged in the body via Magnetic Resonance Imaging techniques as described more fully in *"General Review Article :*

30 *Physics Today, June 1995, p. 17-18"*. However, since the gas phase is

approximately 1000 times less dense (in moles/liter) than the condensed phase of

tissue, its Nuclear Magnetic Resonance (NMR) signal is much weaker than that of

the protons in the condensed biological material. To surmount this, hyper-polarized

^{129}Xenon has been prepared using an optical pumping technique ("Optical Pumping

5   Method": W. Harper et al., Phys. Rev. A29, 3092 (1984)). In this case, the nuclear

magnetization, upon which the magnetic resonance imaging sensitivity depends, can

be increased by 5 orders of magnitude, making the contrast available with the

^{129}Xenon even in the gas phase larger than that from the protons in their equilibrium

room temperature condensed phases. Because the spin is ½, the retention time of the

10   non-equilibrium highly polarized state of the hyper-polarized ^{129}Xenon, frequently

referred to as the spin-lattice relaxation time, T_1, is long enough even at body

temperature for the ^{129}Xenon to persist in the hyper-polarized state for sufficient time

to obtain enhanced images.

         As described above, the production rate of hyper-polarized ^{129}Xenon is

15   relatively low using optical pumping laser techniques, because the polarization is

achieved in the low density gaseous phase. The present invention is directed to

methods to produce high polarization in bulk solid xenon, where large quantities can

be obtained relatively inexpensively. Furthermore, relaxation switches are

introduced which allow the solid polarized material to be warmed up and stored

20   under modest temperature and magnetic field conditions, and finally to be used in

the gaseous phase, or dissolved in liquids while still retaining the high polarizations.

         The equilibrium polarization of the weakly interacting ^{129}Xenon nuclei in the

condensed solid is given by the Brillouin function, where for a spin ½ nucleus, the

polarization P is the following function of B/T, with B the applied magnetic field, T

25   the Kelvin temperature, and k the Boltzmann constant:

$$P = \tanh [\mu(^{129}Xe)B/kT]$$

         Substituting the values of typical temperatures and magnetic fields used in

room temperature MRI, namely about 2 Tesla and 300K, one finds the normal ^{129}Xe

equilibrium polarization equal to about 1.9×10^{-6}. This is smaller than that of the

proton, whose $\mu(^1H)$ is equal to 2.79 nuclear magnetons, resulting in a P at 2 Tesla and 300K of 6.7×10^{-6}.

When ^{129}Xenon is cooled down to a temperature of 10mK, and subjected to an applied magnetic field of about 17 Tesla, both of which are commonly available in modern instrumentation, the equilibrium polarization is equal to 0.45. This more than 5 order of magnitude increase is of great importance, since the sensitivity, and hence detectability and resolution of MRI with these nuclei is proportional to the polarization. By cooling to 5 mK, a feasible prospect, the equilibrium polarization reaches 0.75.

A problem with this method is that even though these polarizations are excellent, the time to achieve them may be enormous, making the method impractical for commercial use. This is because the time to achieve polarization, called the spin-lattice relaxation time T_1, is inherently extremely long at low temperatures (milliKelvin) and high magnetic fields (~ 10 Tesla) for spin ½ nuclei, which are ordinarily relatively isolated from a thermal reservoir necessary for relaxation. The first requirement of a relaxation switch is to provide for decreasing this relaxation time. The second requirement is for the relaxant to be removable. The following relaxation switches have been found to be useful in carrying out the present invention.

A.   Doping Xenon with Paramagnetic Oxygen Molecules:

Oxygen (O_2) is a Paramagnetic molecule which is partly soluble in liquid and solid Xenon. The large electronic magnetic dipole moment couples strongly to the nucleus and can greatly decrease the relaxation time, as has been shown in a large number of experiments since the inception of the NMR technique. A problem is that at the mK temperatures and high magnetic fields, the "motion" of the electronic spins, which is necessary for relaxation, is very small. It was also not known if the solubilities of oxygen in liquid and solid xenon are sufficient to achieve the range of relaxation times needed. We have conducted experiments with various concentrations of oxygen doped xenon, and determined the oxygen concentration, magnetic field and temperature dependencies of the T_1 of ^{129}Xenon, $[T_1(^{129}Xenon)]$.

We also introduced high pressure (8 atmospheres) oxygen to liquid xenon, and utilized appropriate diffusion times (~ 1 hour) for the oxygen gas to enter into the liquid xenon, and subsequent suitable freeze rates (~ 10K/min) of the xenon so that the oxygen is mostly retained. High polarizations greater than 10% were achieved in

5   less than three days at oxygen molar concentrations of about 4%. This already constitutes an effective and economically utilizable situation. It is nevertheless easily improvable by increasing pressure, and varying sample configurations and diffusion times prior to freezing the liquid xenon. A strong concentration dependence was found, as well as an approximately quadratic dependence on

10   magnetic field at high fields. A temperature dependence stronger than linear was obtained in some cases, dependent on how the material was prepared. These dependencies, especially the magnetic field one, can be associated with a degree of freedom called electron "wobble" see *"Electronic Spin Wobble at High Electronic Polarization: J.S. Waugh and C.P. Slichter, Phys. Rev. B37, 4337 (1988)"*, which

15   can account for the satisfactory value of the observed xenon nuclear spin relaxation. Thus, one can achieve high polarizations in a reasonable time, the first requirement of the relaxation switch. The second part of this relaxation switch, in which relaxation is turned off, demands removal of the oxygen without loss of the achieved high polarization. The oxygen relaxation catalyst belongs to a class of impurity

20   relaxants whose volatility exceeds that of xenon. For this situation, we warm up the xenon in the dilution refrigerator, which has provision for thermal isolation from the mixing chamber in a "varitemp" type mode, and pump out the oxygen from the xenon, still in the solid state, at temperatures at which its vapor pressure is very low. The region between 115K and 150K is a good one, since the T_1 of the ^{129}Xenon is

25   acceptably long, and the self-diffusion rate of impurities (oxygen) in the lattice rises exponentially, so that a workable operating point can be found. An alternative is to liquefy the xenon and remove the oxygen by pumping through a membrane which passes oxygen but not the larger xenon molecule. Such a partially permeable membrane may also be useful when removing oxygen from the solid matrix,

30   especially when temperatures are employed at which the vapor pressure of the xenon

is substantial. Use of ultrasonic excitation in both the liquid and solid phase can facilitate the rate of oxygen degassing. The magnetic field is maintained at high values during this process so as to insure the longest possible T_1's at the higher temperatures. The "vari-temp" provision inside the dilution refrigerator is one way

5 of obtaining quick warming without seriously disturbing the dilution refrigerator. In that way, after the oxygen is removed, one can quickly re-cool the polarized xenon and store it for long times, either in the dilution refrigerator or by removing it with a cold-transfer device as more fully described in *"Cold-Retrieval: N. Alexander, J. Barden, Q. Fan and A. Honig, Rev. Sci. Instrum. 62, 2729 (1991)"* and placing it in

10 a separate vari-temp storage cryostat with a 1K-4K temperature capability and a magnetic field in the neighborhood of 10 Tesla, for very long storage times prior to usage, or at liquid nitrogen temperatures, for relatively short term (~day) storage. The teachings of the "Cold Retrieval" article are incorporated herein by reference. An alternative method without the "vari-temp" complication is to collect the gases

15 from the dilution refrigerator mixing chamber, put helium exchange gas in the inner vacuum chamber of the dilution refrigerator, and physically raise the polarized xenon samples to a position along the thermal gradient where the temperature is correct for the oxygen removal operation or for a quick cryopump operation to another cryostat, using holding fields along the path of the polarized gas. After

20 oxygen removal, the xenon is solidified and cooled for storage at temperatures between 1K and 77K, depending on desired storage time. Subsequently, it is warmed in the presence of a high magnetic field, and the polarized gas collected for usage. We outline later various other possibilities for convenient handling and administering of the polarized xenon gas, such as surface flash warming and use of

25 metered capsules. Collected polarized gas may be injected into a solution for rapid medical use.

It should be noted that O_2 is an effective and convenient paramagnetic gas, but other paramagnetic gases, such as NO, may be similarly usable.

B.   Electronic Relaxation - Inducing Impurities from Irradiation

In this case, electron spin relaxants are introduced by irradiating the xenon with ionizing radiation. This can be effected in-situ in the dilution refrigerator with a strong radioactive source, or by provision for an energetic beam of electrons or other particles to impinge on the xenon sample. But by far the easiest way to

5 provide an irradiated sample is to use the cold-transfer device referenced above ("*Cold-Retrieval: N. Alexander, J. Barden, Q. Fan and A. Honig, Rev. Sci. Instrum. 62, 2729 (1991)*").

C. Condensation of the Xenon into a Region with Fixed Magnetic Wires

10 In this case, an array of magnetic wires, or a magnetic mesh, occupies the region where the xenon is to be condensed. It resembles the above case in using proximal contact of xenon with electronically-based magnetism for relaxation toward high polarization. It also requires spin-diffusion. However, for switching off the relaxation, it is in a distinguishable class where after polarization, gasification of

15 the xenon is itself the process for relaxant removal. This may be done by quickly heating and cryopumping to another system, such as an external storage cryostat, or to another cold chamber in the dilution refrigerator, as described in section A. As also mentioned in that section, the presence of a modest magnetic field along the gas conduit path should be assured to maintain the polarization. The magnetic array or

20 mesh can be densely packed thin wires (about 10 - 25 μm diameter) of nickel, nickel-coated aluminum, or other choices of magnetic materials.

D. Dispersed Magnetized Small Particles

Another relaxation switch concept consists of the dispersal of magnetized small particles encapsulated in polymers placed in the xenon, which serve as

25 relaxation agents much as the paramagnetic oxygen did in the first example, except that the magnetic particles contain many magnetic molecules, which can be ferromagnetically coupled so that they retain their magnetization even in a weak external magnetic field. Removal after polarization can be effected by liquefying or gasifying, with the particles settling out away from the gas either gravitationally

30 and/or as a consequence of subjecting them to a strong inhomogeneous magnetic

field. Because the particles are clustered and fairly far apart in the lattice, the relaxation involves both the interaction of the magnetic particles with near xenon neighbors, and spin diffusion which carries polarization to xenon atoms far from the magnetized particles. This can provide a tailor-made magnetic field dependence by adjustment of the particle size and its dispersal, so as to gives greater latitude to the conditions of operating the relaxation switch, both in the polarizing mode and the polarization-maintenance mode.

E.   Dispersal with Stable Free Radicals

The dispersal materials in this case are stable free radicals. A good example is TEMPO as described in *"Stable Free Radicals: TEMPO articles by Bunyatova and by van den Brandt et al, in Nucl. Instrum and Methods A356 (1995)"*, consisting of 2,2, 6,6, -tetra methyl-piperidine-1-oxyl, which has excellent magnetic properties and is used for electron-nuclear dynamically polarized targets for nuclear spin-physics experiments. The above publication is incorporated herein by reference. If these are clustered so as to have a sufficiently large magnetic moment, for example about 10 Bohr magnetons, they can be separated in the liquid phase of the xenon by a very strong B(dB/dz) field. Former work of ours and of others with levitated diamagnetic molecules has shown that values of the product of field and field gradient up to 5×10^9 G^2/cm, more than enough to enough to effect the separation in the liquid, are feasible. After the separation, the usual gasification, as in D above, would follow.

F.   Doping with Molecules which can be Photo-Dissociated in Solution

This form of relaxation switch method involves dissolving into liquid and solid xenon HI, HBr or other photosensitive molecules with respect to HI doping, or described in *"Miyazaki, T, Tsuruta, H. and Fueki, K.J. Phys. Chem 87, 1611 (1983)"*, which is incorporated herein by reference.

G.   Doping Xenon with Mixtures of o-H$_2$ and HD

This method uses doping of xenon with mixtures of o-H$_2$ and HD, in which polarization is transferred cyclically from H to ^{129}Xe by radio-frequency induced forbidden transition adiabatic fast passage (AFP) techniques previously used to

polarize D, and described in *"Enhanced Nuclear Polarization of D in HD"*, *A. Honig and H. Mano, Phys. Rev., B14, 1858 (1976)*; which is incorporated herein by reference.

H.   Electron-Nuclear Dynamic Polarization with Removable Radicals

Here, radicals such as in sections B, E, or F are introduced, but rather than serving as direct nuclear relaxation agents for polarization in very high fields and low temperatures, polarization is achieved through the electron-nuclear dynamic polarization method, in which the electron paramagnets are coupled to the nuclear paramagnets using microwave and radio-frequency excitations. These methods produce high polarization at lower fields and higher temperatures than in the nuclear equilibrium method, but require special relaxation conditions, homogeneous fields and the relaxant may be more difficult to remove. Nevertheless, they constitute a possible relaxation switch operational mode.

The following example illustrates a method for making highly polarized ^{129}Xenon in conjunction with the use of a number of novel relaxation switches.

Example

A large conventional top-loading dilution-refrigerator and magnet system for producing a solid polarized Xenon sample of the present invention utilizes a magnet having a bore of 80mm. A 65 mm diameter cold finger chamber of 30 cm length is contained within the magnet bore and has a volume of about 1 liter. The ^{129}Xenon, with incorporated paramagnetic impurities, such as oxygen, is frozen, and then cooled down to a temperature of about 10 mK in an applied magnetic field of about 15 Tesla. Condensed xenon in that volume provides about 550 usable medical "doses" of 1 hyper-polarized gaseous liter each, on a single polarization production run which typically can require between 1 to 3 days.

A solid polarized xenon sample can be cold-transferred (1K - 4K) out of the dilution refrigerator with the Cold-Transfer Device, after which relaxation catalysts are removed in the manner described herein but from a separate storage cryostat operating at ordinary liquid helium temperatures between 1.5 and 4K, and equipped

with high (>10 Tesla) magnetic fields. This obviates need for vari-temp capability in the dilution refrigerator.

If the dilution refrigerator has a Vari-Temp feature, a thermal disconnect from the mixing chamber can be effected and the sample can be warmed quickly.

5   Then the gas can be cryopumped directly into another cryostat, as long as a retaining field along the pumped path is activated to retain the polarization. The polarized xenon adiabatically follows the guide field.

The cryopumping described above can be into capsules with a small hole for entry and exit of the gas. The volume of the capsule would correspond to that

10   needed for a medical usage dose, for example 2 cm³, corresponding to about 1 liter when gasified. Then, individual polarized gas doses can be retrieved.

The original condensation of xenon can be into capsules with holes, and retrieved with a cold-retrieval device, or separately retrieved as needed from a storage cryostat. The capsules can be on a circular turret, with sequential injection

15   and retrieval using a reusable seal, such as an indium lined cone pair. Methods A,B, F, and H are easily adaptable to this type of production arrangement, but the others can be accommodated by variations of the turret idea as well.

Liquefying and gasifying the solid xenon can be done by direct contact heating, strong infra-red radiative heating, inductive heating from imbedded

20   conductors, or by flash surface heating. The latter could provide a way of obtaining small, approximately measured doses from a bulk polarized solid sample, without using metered capsules.

In one embodiment electron spin relaxants are introduced by irradiating the xenon with ionizing radiation. This is accomplished in-situ in the dilution

25   refrigerator with a strong radioactive source, or by provision for an energetic beam of electrons or other particles to impinge on the xenon sample. A preferred way to provide an irradiated sample is to use the cold-transfer device. This device is placed near an X'ray or other source of ionizing radiation with the sample at temperatures between about 1 and 4K. After the radicals are formed, they persist at the low

30   temperatures. The sample is then transferred into a dilution refrigerator which has a

central access from the top, engaged to the mixing chamber, and then disengaged from the cold-transfer device which is then removed. The sample can now be polarized by the usual way of coming to equilibrium at low (~10mK temperature and high (15-20T) magnetic field. The relaxation switch is subsequently turned off by

5   heating the sample, thereby annealing the defects. This usually occurs in the solid without a large increase of the temperature, but is certainly effected by liquefaction. This form of relaxation switch is an example of a class of relaxants in which additional impurities do not have to be physically extracted, as with doping with paramagnetic oxygen molecules. This presents some additional options for handling

10   the resulting frozen-spin polarized material.

        Another form of relaxation switch method involves dissolving into liquid and solid xenon HI, HBr or other photosensitive molecules. The material, crystallized in a reasonably transparent state, is then irradiated with ultra-violet (and in some cases visible) light, causing radicals to form, which then catalyze the relaxation. After

15   polarization is completed, the photo-induced radicals are eliminated. This acts much as the irradiation with high energy particles proposed for the HD as well as for xenon in the embodiment described above, except it can be turned on by light (UV or visible), and off, by recombination occurring spontaneously in the absence of light, or by infrared light stimulation or annealing heating.

20   In a further embodiment, radicals such as those described above are introduced, but rather than serving as direct nuclear relaxation agents for polarization in very high fields and low temperatures, polarization is achieved through the electron-nuclear dynamic polarization method, in which the electron paramagnets are coupled to the nuclear paramagnets using microwave and radio-

25   frequency excitations. These methods produce high polarization at lower fields and higher temperatures than in the nuclear equilibrium method, but require special relaxation conditions, homogeneous fields and the radicals are more difficult to remove. Nevertheless, it is a possible relaxation switch method. After polarization, the microwave frequency employed is turned off and the electronic paramagnets

30   removed as before. There are combinations of this technique with our other methods

described above for implementing the relaxation switch, which is at the heart of the frozen-spin goal.

     Another embodiment uses doping of xenon with mixtures of o-H_2 and HD, in which polarization is transferred from H to ^{129}Xe by forbidden transition adiabatic fast passage (AFP) techniques previously used to polarize D. As an example, a mole-fraction mixture of about $3X10^{-4}$ o-H_2, 0.2 HD and 0.8 Xenon results in a very high polarization of H in a reasonable time, and a long spin-lattice relaxation time of the H. The H polarization is transferred to the deuterons at low magnetic fields, as described in the original publication *"Enhanced Nuclear Polarization of D in HD"*, *A. Honig and H. Mano, Phys. Rev. B14, 1858 (1976)"*, which is incorporated herein by reference. The transfer cycle can be repeated several times for attaining maximum xenon polarization. If solubility of H_2 (and HD) in Xenon is large enough, the mole fraction of HD can be somewhat increased and the number of AFP polarization transfer cycles reduced. Removal of the hydrogens is not necessarily required, but one can do it if needed by techniques such as described in section A for oxygen removal.

     These examples are not meant to be totally comprehensive, but rather applicable and illustrative. The broad aspect of the invention is the relaxation switch concept. Numerous embodiments have been described, but other methods not explicitly described can be considered as included within the broad scope of the invention.

We Claim:

1   1.   A method for the production and usage of hyperpolarized [129] Xenon

2   which comprises providing solid xenon with either an internal (dissolved) or

3   external (imbedded) nuclear spin relaxant, loading and positioning the solid xenon in

4   a low temperature refrigerator operating in the range of 5 mK to 30 mK with a

5   surrounding magnetic field of between about 10 and 20 Tesla enabling high xenon

6   spin polarizations between about 10% and 50% to be obtained in a time of about 1-3

7   days owing to the properties of the relaxant, separating the xenon from the relaxant

8   or otherwise rendering the relaxant inoperable after polarizing and thereby switching

9   off further relaxation and insuring preservation of the polarization of the xenon in

10   solid, liquid or gaseous form for storage or external use for long times, ranging from

11   weeks to the order of minutes, depending on the usage conditions.

1   2.   A method for the bulk production and usage of hyperpolarized

2   [129] Xenon which comprises:

3   (a)   preparing a sample of liquid xenon with a high concentration of

4   dissolved oxygen by exposing the xenon to high pressure oxygen gas in a limited

5   volume at suitably low liquid xenon temperatures and allowing for the oxygen gas to

6   diffuse throughout the liquid xenon;

7   (b)   freezing and cooling the oxygen-doped xenon down to a temperature

8   of about 100K at a rapid rate, with further cooling at a moderate rate down to mK

9   temperatures in the range 5mK to 30mK;

10   (c)   applying a magnetic field in the range of 10 to 20 Tesla to said

11   oxygen doped xenon to establish an equilibrium polarization between about 10%

12   and 50% for the temperature range of about 10mK to 30mK, and in a time of at most

13   several days;

14   (d)   initiate a relaxation switch-off after (c) above, by removing the

15   oxygen relaxant by a combination of suitable gas separation methods selected from

16   the group consisting of warming and simple mechanical pumping or cryopumping of

17   the evolved gas, ultrasonic stimulation of desorption of the gas, and the use of gas-

18   selective permeability membranes;

19   (e)   re-cooling to liquid helium temperatures for long term storage, or to

20   liquid nitrogen temperatures, for short term usage; and

21   (f)   gasifying the xenon for usage.

1   3.   A method for the bulk production and usage of hyperpolarized

2   ^{129} Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is the result of

4   irradiation of solid cold xenon either in-situ or in an external cold-transferable

5   apparatus wherein after irradiation, the solid is placed in a dilution refrigerator and

6   cooled to mK temperatures and placed in a large magnetic field, until high

7   polarization is obtained;

8   (b)   operate a relaxation switch-off after (a) by heating and annealing out

9   the radiation defects or by causing recombination of the defects by other means such

10   as electromagnetic irradiation; and

11   (c)   re-cool and gasify for usage.

1   4.   A method for the bulk production and usage of hyperpolarized

2   ^{129} Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   an external matrix of paramagnets or magnets in which the solid xenon is imbedded ,

5   with the structure containing the solid xenon placed in a dilution refrigerator and

6   cooled to mK temperatures in the presence of a surrounding large magnetic field;

7   (b)   initiate a relaxation switch-off after (a) by gasifying and thus

8   physically removing the xenon from the structure containing the external relaxant;

9   and

10   (c)   re-cooling and gasifying for usage.

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1   5.   A method for the bulk production and usage of hyperpolarized

2   [129] Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   dispersed magnetic small particles, and the thus prepared solid xenon is placed in a

5   dilution refrigerator and cooled to mK temperatures in the presence of a surrounding

6   large magnetic field until high polarization is obtained;

7   (b)   initiating a relaxation switch-off after (a) by gasifying and thus

8   physically removing the xenon from the structure containing the external relaxant or

9   by sedimenting out the particles from liquid xenon with a centrifuge or force field

10   due to a strong magnetic field gradient; and

11   (c)   re-cool and gasify for usage.

1   6.   A method for the bulk production and usage of hyperpolarized

2   [129] Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   dispersed or dissolved stable free radicals, placing the solid xenon in a dilution

5   refrigerator and cooling to mK temperatures in the presence of a surrounding large

6   magnetic field until high polarization is obtained;

7   (b)   initiating relaxation switch-off after step (a) above by isolating the

8   xenon from the free radicals through warming the xenon and collecting it free of the

9   free radicals via mechanical pumping or cryopumping the xenon into another

10   container directly or through a separating membrane, or by reacting the free radicals

11   with a chemical agent and then collecting the xenon; and

12   (c)   re-cool and gasify for usage.

1   7.   A method for the bulk production and usage of hyperpolarized

2   [129] Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   dissolved molecules such as HI or HBr which can be photo-dissociated by visible or

5   ultraviolet light irradiation in the solid xenon, placing the solid xenon in a dilution

6   refrigerator and cooling to mK temperatures in the presence of a surrounding large

7   magnetic field, until high polarization is obtained;

8   (b)   initiating a relaxation switch-off after step (a) above by ceasing

9   irradiation and allowing spontaneous recombination to occur or by heating to a

10   temperature where rapid recombination occurs among the photo-dissociation

11   products, and separating the xenon from the photosensitive chemicals or their

12   chemical products by mechanical pumping or cryopumping the xenon into another

13   container directly or through a separating membrane and then collecting the xenon;

14   and

15   (c)   re-cool and gasify for usage.

1   8.   A method for the bulk production and usage of hyperpolarized

2   ^{129} Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   dissolved HD and H_2 gas, placing the solid xenon in a dilution refrigerator and

5   cooling to mK temperatures in the presence of a surrounding large magnetic field

6   and cyclically transfer polarization from the H in HD by radio- frequency methods

7   until high polarization is obtained.

8   (b)   initiating a relaxation switch-off after step (a) above by gas

9   separation; and

10   (c)   re-cool and gasify for usage.

1   9.   A method for the bulk production and usage of hyperpolarized

2   ^{129} Xenon which comprises:

3   (a)   the method of claim 1 in which the relaxation agent is in the form of

4   at least one of the group consisting of dissolved paramagnetic material such as the

5   O_2, irradiation products, the dissolved stable radicals, or dissolved photosensitive

6   molecules, in which the solid xenon is placed in a dilution refrigerator, and cooled

7   only to about 50 to 500 mK and placed in a homogeneous magnetic field of a few

8   Tesla, with the polarization of the xenon being attained by microwave irradiation

9   and electron-nuclear dynamic polarization;

10   (b)   initiating a relaxation switch-off after step (a) above; and

11   (c)   re-cool and gasify for usage.

INTERNATIONAL SEARCH REPORT

	International application No. PCT/US99/23647

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6)   : GO1N 29/00

US CL   : 62/630

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   62/630

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,642,625 A (CATES JR. et al) 01 July 1997, see entire document.	1-9
A	US 5,809,801 A (CATES JR, et al) 22 September 1998, see entire document.	1-9

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 JANUARY 2000	0 8 FEB 2000

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